Taken from Amendment filed October 29, 1993
Responding to office action dated June 29, 1993
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been withdrawn. Thus it appears that finality is premature because the issues in this case have not been clearly established.

The Restriction Requirement

The restriction requirement has been made final. Although Applicant does not acquiesce to the requirement, as previously argued, the nonelected claims (9-10, 22-28) have been canceled without prejudice.

The Rejections under 35 U.S.C. 112, first paragraph

The Specification has been objected to and claims 6 and 8-18 have been rejected under 35 U.S.C. 112, first paragraph, with the Office alleging that the disclosure fails to provide an adequate written description of the invention and an enabling disclosure. Applicant respectfully traverses this rejection.

It has been alleged that the Specification does not disclose information required to use any possible host cell, transformation protocols, vectors, suitable cell lines and selectable markers for host cells. It has been further alleged that "the expression of any peptide sequence by any host cell line could not be predicted." Possible mRNA secondary structure and the possible action of host cell proteases were raised as sources of unpredictability.

Without acquiescing to this aspect of the rejection, claims 6 and 21 have been amended to identify Escherichia coli as the host cell in which the random insert/vector population is introduced and expressed. The art is familiar with the use of a number of strains, vectors and selectable markers for expression of heterologous sequences. "A patent need not teach, and preferably omits, what is well known to the art." (Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, C.A.F.C., 1986).

The Examiner has acknowledged that a random oligonucleotide population is enabled, but has alleged that Applicants have failed to describe the expression of the random oligonucleotide population to form polypeptides. There is no statutory requirement that an applicant provide a working example of the invention.

It is inherent that insertion of coding nucleotides within a gene will result in translation of those coding oligonucleotides into protein, i.e. with the production of a fusion protein, provided those sequences are inserted in frame within respect to the coding sequence into which they are inserted. The ordinary skilled artisan recognizes that expression of a fusion protein is dependent on an in-frame fusion. Example IV demonstrates the insertion of coding nucleotides into the minor coat protein gene III of bacteriophage f1. This allows expression of the inserted coding sequences and presentation of the encoded amino acid sequence on the surface of the bacteriophage particle. Fair weight

has not been accorded to the broad enablement in the Specification and in Example IV. As exemplified, the random coding oligonucleotides are inserted within the gene encoding pIII -- there has been no evidence presented that these coding oligonucleotides will not be translated as if they were a natural part of the pIII coding sequence. Thus, the disclosure supports the expression of the random oligonucleotide population as peptide sequences of random amino acid sequence, e.g., within a vector-encoded polypeptide.

The Office has alleged that Applicant has not demonstrated the operability of the invention and that there is "insufficient predictability that any peptide sequence could be expressed in a host and made accessible to antibody," noting possible sources of unpredictability: foreign peptides may be unstable, tandem or duplicative DNA structures may form secondary structures which are unstable or untranslatable, repeated proteins may form aggregates, small peptides are soluble and may be lost during the binding step. It has been further alleged that no examples were disclosed in which random DNA sequences were expressed in the claimed manner and that there is no disclosure as to whether intracellular or cell surface expression is preferable.

The specification, at pages 17-18, bridging paragraph, states that expression of the peptide sequences on the surface of the host cell or bacteriophage is preferred:

> The nucleotide sequence is advantageously inserted in such a way that the peptide sequence encodes by the nucleotide sequence is expressed on the outside surface of the bacteriophage or the host cells...

There is nothing concrete on the record to support a conclusion that the invention would not be operable, particularly in an E. coli host cell, as now claimed. Moreover, the Devlin et al. (1990) Science 249:404-406; Scott and Smith (1990) Science 249:386-390; and Cwirla et al. (1990) Proc. Natl. Acad. Sci. USA 87:6378-6382, already of record, show the recovery of particular epitopes from similar populations of bacteriophage expressing random oligonucleotide sequences. There is no evidence on the record that other epitopes would not be similarly expressed. Thus, it is believed that the Examiner's arguments are effectively rebutted.

While the specification does not present specific exemplification of the expression of a random coding oligonucleotide population and the subsequent detection of a particular epitope, Example V demonstrates the insertion of an exemplary oligonucleotide sequence (encoding an epitope of endoplasmin), its expression within the pIII minor coat protein of bacteriophage f1 and detection with antibody specific for the cognate peptide epitope. There is no sound scientific reasoning on the record as to why any other oligonucleotide coding sequence could not be similarly expressed. Once it is recognized that the f1 minor coat protein can tolerate insertion of such a relatively

short insertion and that a heterologous epitopic sequence is expressed in a form recognized by the cognate antibody, then it is expected that other epitopic sequences would be similarly expressed and displayed. There is no reason on the record that the expressed endoplasmin epitope is unique. Clearly, the inserted endoplasmin epitopic sequence was too small to disrupt minor coat protein folding. the art knows to avoid stop codons in the inserted oligonucleotide sequences. Even if rare sequences are not expressed, the majority of the population will be expressed.

The Declaration of George Pieczenik, submitted on May 15, 1992, as Exhibit E, demonstrated the specific binding of an endoplasmin epitope-specific antibody to a recombinant f1 bacteriophage expressing the cognate endoplasmin epitopic sequence is shown, and the Supplementary Pieczenik Declaration, submitted with the current amendment, states that this work was done prior to July 26, 1990.

With respect to the breadth of "host cells," Applicant has amended claim 6 to identify Escherichia coli as the host cells in which the recombinant random coding oligonucleotides are to be expressed. This amendment is clearly supported by the disclosure. It is believed that this claim amendment makes this aspect of the rejection moot, but Applicant reserves the right to prosecute the withdrawn claims in another application.

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closely related to the invention of Group II in that the antibodies of Group III reacts with the peptides of Group II, which are encoded by the oligonucleotides of Group III. The Invention of Group IV combines the antibodies related to the Invention of Group III and the peptides of Group II. Thus, the inventions allegedly distinct are so closely intertwined that Applicant respectfully requests that all the claims in the instant case be examined as a whole.

The Rejections under 35 U.S.C. 112, first paragraph

The Specification has been objected to and claims 1-28 were rejected under 35 U.S.C. 112, first paragraph, with the Office Action alleging that the disclosure fails to provide an adequate written description of the invention and fails to provide an enabling disclosure. Applicant respectfully traverses this rejection.

The Examiner has acknowledged that a random oligonucleotide population is enabled, but has alleged that Applicants have failed to describe the expression of the random oligonucleotide population to form polypeptides. Applicants point out that it is inherent that insertion of coding nucleotides within a gene will result in translation of those coding oligonucleotides into protein, i.e. with the production of a fusion protein. Example IV demonstrates the insertion of coding nucleotides into the gene III of

bacteriophage f1; gene III encodes pIII, a minor coat protein. It naturally follows that the inserted coding sequences will be expressed and presented to the desired antibody on the surface of the bacteriophage particle. It is a mischaracterization of the disclosure to allege that Example IV "merely enables the construction of a random peptide DNA library." As exemplified, the random coding oligonucleotides are inserted within the gene encoding pIII -- there has been no sound scientific reasoning or evidence presented that these coding oligonucleotides will not be translated as if they were a natural part of the pIII coding sequence. Thus, it is believed that the disclosure dces support the expression of the random oligonucleotide population as peptide sequences of random amino acid sequence, e.g. within a vector-encoded polypeptide.

The Office has alleged that Applicant has not demonstrated the operability of the invention and that there is "insufficient predictability that any peptide sequence could be expressed in a host and made accessible to antibody." He has noted possible sources of unpredictability: foreign peptides may be unstable, tandem or duplicative DNA structures may form secondary structures which are unstable or untranslatable, repeated proteins may form aggregates, small peptides are soluble and may be lost during the binding step. The Examiner has further alleged that no examples were disclosed in which random DNA sequences were expressed in the

claimed manner and that there is no disclosure as to whether intracellular or cell surface expression is preferable.

As a first matter, Applicant has indicated that expression of the peptide sequences on the surface of the host cell or bacteriophage is preferable. See, e,g, pages 17-18, bridging paragraph, which states:

> The nucleotide sequence is advantageously inserted in such a way that the peptide sequence encodes by the nucleotide sequence is expressed on the outside surface of the bacteriophage or the host cells...

The Examiner has presented a number of speculative sources of unpredictability in expression of the random oligonucleotide population, but there is nothing concrete cited to support a conclusion that the invention would not be operable. Therefore, the burden for doubting Applicant's broad enabling statements established by In re Marzocchi, 169 U.S.P.Q. (C.C.P.A. 1971) has not been met and the rejection has not been made proper.

While the specification does not present specific exemplification of the expression of a random oligonucleotide population and the detection of a particular epitope, Example V presents the successful demonstration of the insertion of a particular oligonucleotide sequence encoding an epitope of endoplasmin, its expression within the pIII protein of bacteriophage f1 and detection with antibody specific for the